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ORIGINAL ARTICLE

Administration of contrast media just before cisplatin-based chemotherapy increases cisplatin-induced nephrotoxicity

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Summary

Purpose: There is a clinical need to predict the probability of cisplatin-induced nephrotoxicity (CIN) in order to make decisions about patient management and relevant preventive measures. The purpose of this study was to develop a risk prediction methodology of CIN.

Methods: 197 consecutive cancer patients, whose serum creatinine was measured at least 48 h before every cycle of cisplatin-based chemotherapy, were included in the study. Demographic and clinical data were collected from the patient medical records. Renal function was evaluated at least 48 h before treatment (day 0) of each cycle, based on the Modification of Diet in Renal Disease (MDRD) formula. CIN was defined as a decrease of ≥ 25% in glomerular filtration rate (GFR) compared to baseline GFR values.

Results: The mean age of the study population was 54.5±9.6 years. Fifty-eight patients (29.4%) whose GFR had decreased by at least 25% compared to baseline values formed the CIN group, and the remaining 139 patients formed the non-CIN group. No significant differences were noted between the CIN and non-CIN groups in terms of age, gender, body mass index and smoking history. Metastatic disease was similar in both groups (p=0.86). History of hypertension (p=0.81), diabetes mellitus (p=0.72), and cardiovascular disease (p=0.58) were similar in the two groups. Chemotherapeutic agents used concurrently with cisplatin were similar in both groups. Significantly more radiologic examinations using contrast media were performed in the CIN group compared with the non-CIN group (p=0.01). In patients exposed to contrast media within a week before cisplatin administration, the risk of CIN was 2.56-fold higher (95% CI 1.28-5.11) than in patients without such exposure (p=0.009).

Conclusion: In patients with exposure to contrast media within a week before cisplatin administration, the risk of CIN was significantly higher than in patients without such an exposure. No additional risk factors for CIN were found in this retrospective observational study.

Key words: chemotherapy, cisplatin, contrast media, nephrotoxicity

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Introduction

Cisplatin is a potent and an effective chemotherapeutic agent used to treat various types of cancers including sarcomas, some carcinomas (e.g. small cell lung cancer, ovarian cancer), lymphomas, and germ cell tumors [1]. The most important dose-limiting adverse effect of cisplatin is renal tubular dysfunction manifested as a decline in the GFR and a cumulative impairment in renal function [2]. Nephrotoxicity with cisplatin-based chemotherapy regimens had been observed in more than 50% of the cases in some of the early trials prior to the use of intensive hydration regimens [2]. Despite aggressive hydration, which is routinely applied in the clinic, renal dysfunction still continues to occur [3]. Therefore, several attempts have been made to reduce nephrotoxicity, either by hydration and forced diuresis (administration of aggressive hydration, mannitol, furosemide) or by an alternate method of administration of cisplatin. Risk factors for cisplatin nephrotoxicity include high peak plasma free platinum concentrations, previous exposure to cisplatin, preexisting kidney damage, and the concomitant use of other nephrotoxic agents [4,5]. In an analysis of 400 patients investigating risk factors of nephrotoxicity De Jongh et al. reported that older age, smoking, female gender, hypoalbuminemia, and paclitaxel co-administration are potentially associated with CIN [6,7].

The incidence and severity of renal toxicity increases with repeated usage of cisplatin-based chemotherapy and CIN can consequently become irreversible. As a result, cisplatin discontinuation is generally indicated in those patients who show evidence of progressive renal impairment. There is a clinical need to predict the probability of CIN in order to make decisions about patients' management and take preventive measures. The purpose of the present study was to develop a risk prediction methodology of CIN due to lack of clear results from previous studies.

Methods

One hundred and ninety-seven consecutive cancer patients treated with cisplatin-based combination chemotherapy in the Department of Medical Oncology of the Ankara Numune Training and Research Hospital between January 2007 and December 2010 were included in this study. These patients had serum creatinine measured at least 48 h before each cycle of cisplatin-based chemotherapy. Demographic and clinical data including age, performance status, tumor characteristics and co-morbid diseases were collected from medical records. Patient performance status (PS) was evaluated by using the Eastern Cooperative Oncology Group (ECOG) scale. Toxicity evaluation was conducted according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Cisplatin was administered once every 3 weeks at doses of 75-80 mg/m^2 at a 20-40 mg/m^2/h infusion rate. Cisplatin was administered concurrently with either vinorelbine, paclitaxel, etoposide or gemcitabine. In patients with contrast-enhanced examinations omnipaque 100 ml (osmolarity 0.64 OSM/kg H_2O at 37^{o}C), a non ionic low-osmolarity contrast medium was used. Renal function was evaluated at least 48 h before treatment (day 0) of each cycle; GFR was calculated based on the MDRD formula which estimates 4 variables: serum creatinine, age, race and gender: 186 x (serum creatinine [mg/L$^{-1.154}$] x (age [years])$^{-0.203}$x (0.742 if female) x (1.210 if of African descent). CIN was defined as a decrease of at least 25% in GFR compared to baseline GFR values. Patients with baseline GFR < 60 ml/min were excluded from the study.

Hydration protocol of cisplatin-based chemotherapy

Intravenous infusion of 500 ml saline in 60 min was followed by infusion of gemcitabine, paclitaxel, vinorelbine or etoposide in another 500 ml of saline. Then, cisplatin infusion with 1000 ml saline was given in 4 h, followed by another 500 ml saline (at least 2500 ml saline in total). Intravenous magnesium sulfate 3 g were administered as standard treatment to every patient. All patients were administered antiemetics.

Statistics

Statistical analyses were performed by using SPSS for Windows version 18.0 (SPSS, Chicago, IL). Patients were divided into two groups according to whether they developed nephrotoxicity. Baseline characteristics of patients who developed CIN were compared

Table 1. Baseline characteristics by cisplatin nephrotoxicity

Characteristics	*Cisplatin nephrotoxicity*		*p-value*
	Yes N (%)	*No* N (%)	
Total	58 (100)	139 (100)	
Age (years)			
<50	18 (31.0)	44 (31.6)	0.87
≥50	40 (69.0)	95 (68.4)	
Sex			
Female	8 (16.0)	19 (13.6)	0.57
Male	50 (84.0)	120 (86.4)	
Body mass index (kg/m^2)			
< 30	24 (41.3)	54 (38.8)	0.47
≥ 30	34 (58.7)	85 (62.2)	
Smoking			
No	11 (19.0)	25 (17.9)	0.88
Yes	39 (67.2)	91 (65.5)	
Ex-smoker	8 (13.8)	23 (16.6)	
ECOG PS			
0	3 (5.1)	11 (7.9)	0.52
1	39 (67.2)	99 (71.2)	
≥ 2	16 (27.7)	29 (20.9)	
History of NSAID usage			
No	40 (69.0)	99 (71.2)	0.23
Yes	18 (31.0)	40 (28.8)	
History of bisphosphonate usage			
No	56 (96.6)	135 (97.1)	0.83
Yes	2 (3.4)	4 (2.9)	
Hypertension			
No	52 (89.7)	121 (87.0)	0.81
Yes	6 (10.3)	18 (13.0)	
Diabetes mellitus			
No	53 (91.4)	123 (88.5)	0.72
Yes	5 (8.6)	16 (11.5)	
Congestive heart failure			
No	56 (96.6)	136 (97.9)	0.58
Yes	2 (3.4)	3 (2.1)	
Type of cancer			
Lung	40 (69.0)	98 (70.5)	0.35
Pancreas	16 (27.7)	38 (27.4)	
Stomach	2 (3.4)	3 (2.1)	
Metastasis at presentation			
No	15 (25.9)	39 (28.1)	0.86
Yes	43 (74.1)	100 (71.9)	
Cisplatin combination with			
Gemcitabine	28 (48.3)	68 (48.9)	
Navelbine	6 (10.3)	10 (7.2)	0.79
Taxanes	5 (8.6)	13 (9.4)	
Etoposide	19 (32.8)	48 (34.5)	
Anemia			
No	44 (75.9)	110 (79.2)	0.46
Yes	14 (24.1)	29 (20.8)	
Hypokalemia (serum K < 3.5 mEq/L)			
No	3 (5.2)	5 (3.6)	0.55
Yes	55 (94.8)	134 (96.4)	
Hypoalbuminemia (serum albumin < 3.5 g/dl)			
No	8 (13.8)	22 (15.8)	0.11
Yes	50 (86.2)	117 (84.2)	
History of administration of contrast media			
No	15 (25.9)	61 (43.8)	0.01
Yes	43 (74.1)	78 (56.2)	

Table 2. Baseline characteristics according to contrast exposure

Characteristics	*Contrast exposure*		
	Yes N (%)	*No* N (%)	*p-value*
Total	121 (100)	76 (100)	
Sex			
Female	18 (14.9)	9 (11.8)	0.35
Male	103 (85.1)	67 (88.6)	
History of NSAID usage			
No	86 (71.1)	53 (69.7)	0.11
Yes	35 (28.9)	23 (30.3)	
History of bisphosphonate usage			
No	118 (97.5)	73 (96.1)	0.42
Yes	3 (2.5)	3 (3.9)	
Hypertension			
No	106 (87.6)	67 (88.2)	0.54
Yes	15 (12.4)	9 (11.8)	
Diabetes mellitus			
No	107 (88.4)	68 (89.5)	0.50
Yes	14 (11.6)	8 (10.5)	
Congestive heart failure			
No	120 (99.2)	73 (96.1)	0.16
Yes	1 (0.8)	3 (3.9)	
Type of cancer			
Lung	80 (66.1)	50 (65.8)	0.24
Pancreas	38 (31.4)	24 (31.5)	
Stomach	3 (2.5)	2 (2.6)	
Metastasis at presentation			
No	83 (68.6)	50 (65.8)	0.17
Yes	38 (31.4)	26 (34.2)	
Chemotherapy combination with			
Gemcitabine	58 (47.9)	35 (46.1)	0.21
Navelbine	11 (9.1)	5 (6.5)	
Taxanes	10 (8.3)	11 (14.5)	
Etoposide	42 (34.7)	25 (32.9)	

with non-CIN group with x^2 test (for categorical variables) or two-sample T-test (for continuous variables). Logistic regression analysis was used in order to test baseline parameters for their prognostic value regarding toxicity. Log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided p-values of <0.05 were considered statistically significant.

Results

The mean age of 197 patients was 54.5±9.6 years. Fifty-eight patients (29.4%) whose GFR decreased by at least 25% compared to baseline GFR were included in the CIN group, and the remaining 139 patients were included in the non-CIN group. Cisplatin-based chemotherapy was used mostly in patients with non-small cell lung cancer (N=98), pancreatic cancer (N=54) and small cell lung cancer (N=40) in this study population. Distribution of the disease types did not differ significantly between the CIN and non-CIN groups. Baseline demographic and clinical characteristics are listed in Table 1. There was no difference in terms of age, gender, body mass index and smoking history between the two groups. Baseline mean serum creatinine levels were 0.84±0.2 and 0.88±0.2 in the CIN and non-CIN groups, respectively (p=0.12).

The baseline GFR values as calculated by the MDRD formula were 98±26 ml/min in the CIN group and 94±24 ml/min in the non-CIN group (p=0.22). The mean serum albumin levels were 4.0±0.6 g/dl in the CIN group and 4.1±0.7 g/dl in the non-CIN group (p=0.11). The mean serum uric acid and potassium levels were similar between the two groups.

Metastatic rate was similar in both groups at the the time of diagnosis (p=0.86). Also, history of hypertension (p=0.81), diabetes mellitus (p=0.72), and cardiovascular disease (p=0.58) were similar in the two groups. Chemotherapeutic agents used concurrently with the cisplatin chemotherapy were similar in the CIN and non-CIN groups (Table 1). Median cisplatin cycles were 4 (range 1-12) in both groups. Mean total cisplatin dose was 325±143 mg/m^2 and 362±180 mg/m^2 in CIN and non-CIN groups, respectively (p=0.30). For response evaluation 121 patients (61.4%) had chest and abdominal CT scan. The mean age of the patients with contrast exposure was 54.5±0.9 years, whereas it was 54.4±1.0 years in the non-contrast exposure patients (p=0.91). The pre-contrast exposure GFR value was 101±2.6 ml/min, whereas the post-contrast exposure GFR was 86.5±3.2 ml/min (p=0.01). Radiologic examinations with contrast media were performed more frequently in the CIN group as compared to the non-CIN group (p=0.01). In patients exposed to contrast media within a week before cisplatin administration, the risk of CIN was 2.56 (95% CI 1.28-5.11) fold higher than in patients without exposure to contrast media (p=0.009) (Figure 1). CIN was seen in 45.6% of the patients exposed to contrast media within a week before cisplatin administration and in 19.4% of the patients not exposed to contrast media (p=0.01). Two patients in the CIN group required hemodialysis and both these patients were exposed to contrast media within a week before the administration of cisplatin.

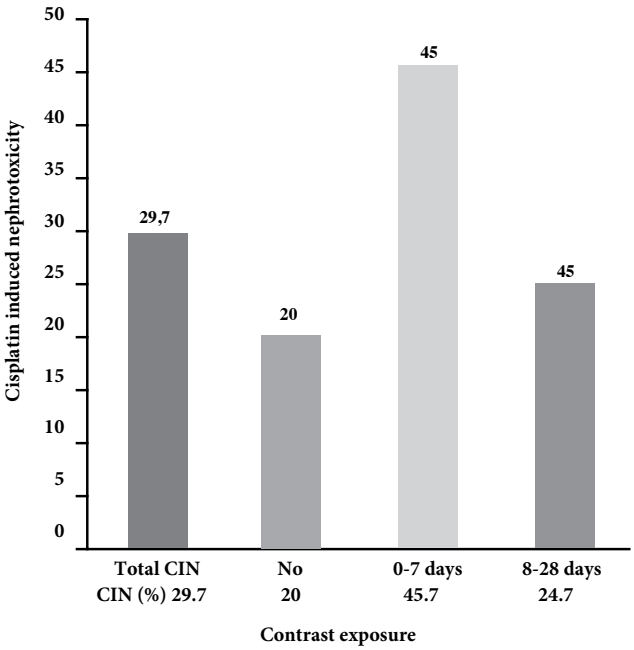

Figure 1. Rate of cisplatin-induced nephrotoxicity (CIN) according to contrast exposure (p value is 0.01 between no contrast exposure and contrast exposure between 0-7 days; p value is 0.02 between contrast exposure 0-7 days and 8-28 days).

Discussion

In the present study, nephrotoxicity developed in 29.4% of the 197 patients treated with cisplatin-based chemotherapy. In both groups, a median of 4 cycles of cisplatin-based chemotherapy was given every 3 weeks with a median cisplatin dose of 320 mg/m^2. Chemotherapeutic agents administered concurrently with cisplatin were similar in the CIN and non-CIN groups. Previously described potential risk factors for CIN such as hypoalbuminemia, hypokalemia, smoking history, gender, and older age, were also investigated in this study, but no relationship with nephrotoxicity was found with any of the aforementioned parameters. This retrospective observational study showed that exposure to contrast media within a week before administration of cisplatin increased the risk of CIN by 2.56 fold. To our knowledge, this study is the first to show the relationship between CIN and cisplatin-based chemotherapy.

Cisplatin nephrotoxicity generally manifests as a reduction in GFR due to renal tubular dysfunction and the risk of nephrotoxicity increases with repeated cycles of chemotherapy [8]. Several mechanisms are responsible for renal dysfunction following cisplatin administration. These mechanisms are tubular epithelial cell toxicity, vasoconstriction in the renal microvasculature and pro-inflammatory effects of cisplatin [9]. More than 50% of the drug is excreted in the

urine in the first 24 h following cisplatin administration and the concentration of platinum achieved in the renal cortex is several fold greater than in plasma and other organs [9]. Because of its low molecular weight, cisplatin is freely filtered in the glomerulus [10]. Cisplatin primarily injures the S3 segment of the proximal tubule, causing a decrease in the GFR [11]. Cisplatin can also cause vasoconstriction in the renal microvasculature, thus leading to decreased renal blood flow [12]. Contrast media can precipitate CIN. Renal vasoconstriction is a common finding of contrast nephropathy which is mediated by contrast-induced release of endothelin and adenosine and by the high osmolality of the contrast agent [13,14]. Besides, contrast media can cause tubular injury as a result of direct cytotoxic effects or in association with the generation of oxygen free radicals [15]. Because both cisplatin and contrast media can cause nephrotoxicity by same mechanisms, it is not surprising that CIN develops more frequently in patients exposed to contrast media as seen in our study. Raschilas et al. [16] reported severe acute renal failure after administration of contrast media in a patient treated with cisplatin. Oymak and colleagues [17] also reported the induction of an irreversible acute renal failure following intraperitoneal cisplatin chemotherapy and contrast media injection in a woman treated for ovarian cancer.

Despite aggressive hydration with saline, which is routinely applied in the clinic like in our study, nephrotoxicity still occurs. Therefore, several preventive attempts should be done to reduce CIN. Mannitol is frequently used to induce diuresis; however there is no convincing data that mannitol and other diuretics may attenuate cisplatin nephrotoxicity [18]. N-acetylcysteine, a thiol derivative, may have some role in preventing cisplatin nephrotoxicity in high risk patients, but there are contradictory results in the prevention of contrast nephropathy [19,20]. Benoehr et al. [21] reported that theophylline may prevent CIN in a small clinical trial.

Due to the high incidence of CIN with the currently used platinum compounds, new less nephrotoxic platin formulations have been investigated. Jehn et al. [22] reported that liposomal formulation of cisplatin (lipoplatin) reduces renal toxicity compared to conventional cisplatin. In another study, no nephrotoxicity was observed in the second-line therapy for small cell lung cancer with a platin derivative picoplatin [23]. Until less nephrotoxic compounds of platin derivatives are widely available, it seems suitable to avoid concomitant nephrotoxic agents and volume depletion during conventional cisplatin treatment.

Due to the lack of large, significant studies, optimal therapy to prevent CIN remains unclear. Radiologic procedures, mostly with contrast media, are widely used to evaluate the response to chemotherapy. In conclusion, we suggest that radiographic procedures with intravenous contrast material should be delayed for at least 1 week in patients receiving chemotherapy with cisplatin.

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Introduction

In Greece, malignancies constitute the second cause of mortality (23%) and the third of morbidity (9.4%) with apparently increasing trends. During their treatment, patients suffering from cancer seem to have a series of ethic and practical dilemmas, intermingled with the way the delivery of health resources is practiced. The function of an oncologic board is imposed for the above mentioned reasons before the application of any kind of treatment. The oncologic board must be composed by surgeons, medical oncologists, radiation oncologists and pathologists.

Methods, Results and Discussion

A literature review has recently been carried out. Internet databases were searched using key words such as oncologic board, medical legislation and medical ethics.

In Greece the institutional framework of an oncologic board is defined by the regulations of Medical Deontology 25/1955(A171), articles 27, 28, 29 and 30 (when and where it is convoked, its powers etc), the Declaration of Amsterdam (briefing, patients' rights), the law 3209 (24 -12-2003, page 5206, paragraph 2, over the formation and operation of the oncologic board of the Hospital) [1], and the Medical Code of Deontology /2005(briefing and patient's acceptance). Briefing is not a simple procedure, especially for those who suffer from cancer and constitute a social stigma. Moreover, the convocation of the board is not accompanied by a written binding deduction.

It is underlined that most of the time participants of an oncologic board discuss about patients without having seen them, while they have to take fundamental decisions about their health. It is thus understandable that quite often therapy has to be changed according to new data. That is to say that social factors and demographic data of each patient have to be taken into consideration.

It is clear that the physician is not legally obliged to heal the patient but to do his best to provide his services assiduously according to the scientific progress made up to that date.

Human life is protected by the Law in any form and under any circumstances. A fatal disease neither negates nor restricts the staff's obligation to give the patient the proper care.

Generally speaking, physicians and nurses have an increased obligation to take care of patients and this is due not only to the possible danger which threats human life and health but also to the relation based on the confidence between the patient and the doctor.

Consequently, doctors have to do their job according to the regulations and their knowledge of the technological advances in medicine (*lege artis)*, otherwise compensation rights may be asked by the patients if health damage is proved or if doctors or health staff have not fulfilled their duties [2].

Furthermore, it is crucial to point out that patient' rights regarding legal matters and the relationship between physicians and patients are described in Law texts or in Declarations such as the one of Lisbon (Table 1).

According to the present legislation, life is the milestone of our civilization and therefore it is worth protecting it under any circumstances, even if the patient or his relatives think otherwise. According to the article 299 of the Penal Code, whoever takes human life is charged with homicide and he is sentenced to life imprisonment or he is put in jail for 5 to 20 years.

The first contemporary Greek Medical Deontology Code (Greek Government Gazette 171-A-16-7-55) [3] refers to the patients' rights in its articles 8

Table 1. Patients' human rights (Declaration of Lisbon)

The patient has the right to choose his physician freely.
The patient has the right to be cared for by a physician who is free to make clinical and ethical judgments without any outside interference.
The patient has the right to accept or to refuse treatment after receiving adequate information.
The patient has the right to expect that his physician will respect the confidential nature of all his medical and personal details.
The patient has the right to die in dignity.
The patient has the right to receive or to decline spiritual and moral comfort including the help of a minister of an appropriate religion.

and 9. The Penal Code points out that omissions or negligence during daily medical practice are considered to be 'punishable' (articles 300, 301 and 302) [4].

Social instructions are based on this spirit in the Law 2071-92, articles 47, 61, and 62, as far as the patients' rights in hospitals are concerned.

The Law 2519-1997, Greek Government Gazette 165, about Regulations in the National Health System emphasizes in his first article the civilians' rights to benefit from health services. The legislator also recommends the creation of a special committee with specific responsibilities for the protection of patients. A committee will also be set to facilitate the communication between doctors and patients.

The independent management by an advocate of health and social solidarity is established with the Law 3293-2004. This one is incorporated to an independent authority managed by ombudsman who has already provided services to any civilian in need of public health services. His jurisdiction has to do with the rehabilitation and the protection of any civilian and the transmission of the case to the relevant Ministry. The advocate for health and welfare examines the legality of individual administrative acts or omissions which may occur by the Health sector and which is pointed out by affected citizens. His intervention may appear after the civilians have submitted their case to the implicated Health Service. Furthermore, this advocate has the right to mediate in cases which concern the Ministry of Health and Social Solidarity, the regional management, insurance organizations, and pension/health care funds, general or specialized hospitals, psychiatric hospitals, health centers, regional and rural clinics etc.

One essential criterion to characterize a medical act as correct is the compliance with obligations by physicians as far as patients are concerned, according to the Medical Deontology and the respect of human life as it has already been mentioned.

In medicine, a clear distinction is often done between technical errors and errors of judgment.

Both errors can be made either during the period of diagnosis or during the treatment period, which consequently could damage the patient's health or even threaten his life. In addition, other errors can be identified:

- Unnecessary errors, i.e. the ones doctors or nurses are not responsible for as they have done their best to fulfill their mission.
- Liable errors, i.e. the ones doctors and nurses are responsible for as they have made mistakes by omitting asking for the appropriate medical tests or by not achieving what can be done to relieve patients.

An accident is characterized as being random and unpredictable and as one which can damage the patient while doctors and nurses are not responsible for.

The failure of a medical action is specifically defined according to its result. An unsuccessful medical action has as a consequence to hurt the patient either by the non accomplishment of the therapy or by the existence of side effects regardless of the patient's restoration from his initial health condition.

The civil medical liability is divided into two categories:

1) The conventional one, which is the agreement made by a patient and a physician about the services provided by the latter of the two. It's in fact a deal with a work contract if the doctor's services are remunerated for a short or a long period of time and with a project contract if the doctor's services are provided for a specific medical act. As a result, a refund can be asked if the agreement is not respected.
2) The tortious one. In this case, the conditions asked for a refund are not only foreseen in the article 914 AK but also in some specific regulations. Here are some of the conditions: a) the irresponsible attitude and the lack of consciousness shown by the physician as defined by the Law and the common sense; b) the lack of knowledge, skills and attention which could have provoked a disastrous result; c) the negligence which could cause death or damage; d) the connection between practice and result or omission of medical service and result.

It's up to the judge to decide whether there is malfeasance or if damage is caused by accident, estimating the facts which occur in each case.

It is sometimes possible the damage caused to the patient to concern only his fortune, for instance when the patient has to spend a lot of money for his medi-

cation etc. The physician's specialty is taken into account too as the expenses may be higher due to this fact.

From the above-mentioned, legal penalties or excessive compensation may constitute a serious handicap to medical science and may not boost the right practice of it. The so called 'defensive medicine' is then put forward, i.e. the doctor - in a effort to protect himself against possible charges for negligence - orders unnecessary medical exams which may produce evidence of his innocence but certainly not promoting the patient's welfare. Finally it is needed to point out that, despite the amendments made in the Medical Law (Law 3418/ 2005) to protect patients, same proved inadequate due to the complexity, and inconsistency of Greek legislation [2].

According to the District European Bureau of World Health Organization the content of the patients' briefing should include:

- The procedures concerning the diagnosis.
- The diagnosis itself.
- The various options of treatment, their advantages

Table 2. Greek Medical Code of Deontology 2005; Patient's briefing

Article 1 (meanings, definitions and applications) paragraph 48:

With the word 'intimate' we mean relatives by blood or marriage, foster parents and foster children, husband and wife, the long term companions, siblings, siblings' long term companions or spouses, commissioners and all those who are under judicial support.

Article 9 (doctor's obligations towards his patient), paragraph 1:

Priority is given to the protection of the patient' s health.

Article 11 (briefing obligations):

1. Physicians' duty is to tell the truth. Patients must be fully informed about their real condition, the application and the results of the suggested medical services, the consequences, the risks and complications of its applications, the alternative options and the rehabilitation time which may be needed. Taking then everything into consideration, patients can make up their mind and decide what the best is for them.
2. Physicians respect people's desire not to be informed. In this case, patients have the right to designate a person of their choice so as to be informed about their condition, the results of the suggested medical acts, the consequences and the possible dangers of them.
3. Special attention must be paid when patients are informed about surgical operations such as transplants, assisted reproduction interferences, gender change or rehabilitation and cosmetic surgeries.
4. If patients have not the ability to consent on a medical act, physicians should inform them as much as it is feasible. Other persons who have the authority to take decisions according to the next article must be informed too.

Article 12 (patient's consent):

1. The physician has not the right to act without prior patient's consent. For the rest of the cases, when a person has not the ability to take any decision, it is for the judge to decide or for the designated person what could be done. In each case, the physician must try to ensure the voluntary participation and cooperation of the patient and especially of the one who can comprehend his condition, the dangers and consequences of the medical intervention.
2. Not only the addition of all the positive elements of the autonomy of other societies but also the beneficial influence of the Greek family will lead to face the problem of patients' briefing suffering from malignancies more effectively according to the Greek mentality and not according to the adoption of other informative ways of other societies.
3. Briefing, informed consent and the respect of the patients' autonomy constitute fundamental ethical issues of the relation between doctor and patient. Patients' autonomy has been characterizes as the most common practice in medical ethics [7]. In hospitals, patients' briefing is not an easy matter, especially for the ones who suffer from a fatal disease or connected with a social stigma. Hiding a painful truth is common practice. A clear change has only been noticed in Western societies the last 30 years [8, 9]. The reason of hiding the truth is to give people hope which is crucial for their psychology [9-11].

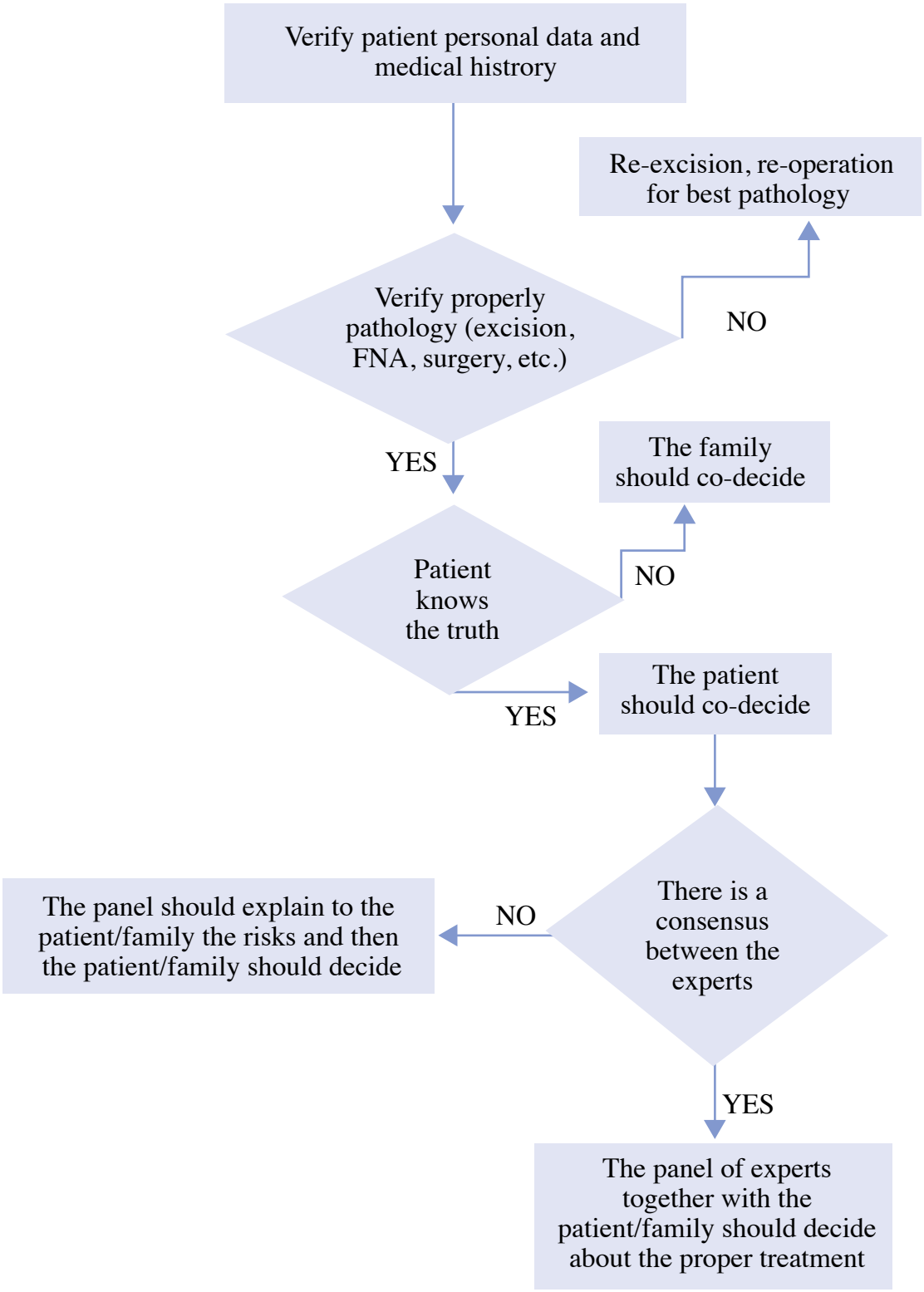

Figure 1. Flow chart with the suggested procedure involving the patient/family.

and disadvantages and their possible consequences.
- The eminent dangers or not of the therapy or the denial of it.
- The procedure of the treatment, its duration and the patients' suffering because of it.
- The prognosis.
- The results and the side-effects of the medication and their interaction with other drugs.
- The status of health and the way of life after treatment.

The Declaration of Amsterdam [5] about patients' rights in Europe in 1994 states that patients should be fully aware of:
- Their health condition and the medical data concerning their disease.
- The suggested medical procedures along with their benefits and drawbacks.
- The alternative options with their results on the diagnosis, the precognition and the course of treatment.

The Code of Medical Deontology, voted in the Greek Parliament, sets rules in our country for the first time which deal with the physician's obligations to inform his patients (Table 2) [6-10].

However, this regulation is not fully compatible to the Greek mentality [11].

In the last 30 years, the way of informing patients has radically changed from a protective concealing to fully revealing the truth condition to the patient. This change results to the human's respect and autonomy and is more intense in North America and North-West Europe. Hiding the truth from cancer patients is still in use in many countries including Greece. A great number of factors contribute to the different policies of information. Kallergis G. reported the methodology by which the information can be disclosed to the patient about his status. The method depends upon the character of each patient [12-15]. The communication among family members should be the determining factor for choosing the appropriate approach for informing them [16, 17].

In societies, such as the Greek one, where the family bonds are still strong, there is a tendency to overprotect sick people from the bad news as the whole family faces the problems and not only one of its members. Consequently, the relation between patient and doctor is transformed to a relation between family and doctor. This is a Greek reality and it has not been taken into account by the Code of Medical Deontology.

The Code of Medical Deontology which was voted unanimously by the members of the Parliament on 8 November 2005 deals with matters of briefing and patient's consent for the first time. The Code requires the patient's full briefing of his condition apart from the cases where the patient does not choose to be informed or he is not capable of being so [18]. On the other hand, it is well known that the patient is not aware of his condition, particularly after the diagnosis, and only his close relatives are informed. There is then a contradiction between the new Medical Code of Deontology and the traditional practice in our country [19, 20].

In a study made at the 'Aretaieion' University Hospital, only 23% of the patients' relatives suffering from cancer considered that they must be informed of their condition, while 73% of the health staff believed that they should be aware of their disease [21]. Moreover, 89% of the health staff considered that the relatives must be informed too. When health care providers communicate with their patients, they avoid using the word 'cancer' even if they know it and 62 % have difficulties in having a clear conversation with the patients when forecast issues have to be put forward. Forty one percent believed that briefing may lead to the patient's disappointment and isolation.

On the other hand, 71% of the health care providers were convinced that a basic element for the healing process is revealing the truth. Finally, most of the health staff considered telling the truth is the doctor's responsibility [22, 23]. A review of related studies from 1971 to 1987 showed that Greek doctors insist on hiding the diagnosis from their patients and hardly speak of their forthcoming death. On the contrary, more and more patients demanded a full briefing [24]. In a recent Greek poll among 1500 doctors in oncology or general hospitals, 22% revealed the truth and 76% preferred to inform the patient relatives. It is obvious that things tend to change step by step [19, 25, 26].

The change in the briefing procedure is related

with the change of social structures. This change of attitude has begun in the Western societies and demands the person's respect and autonomy even when it comes to medical decisions [27]. This attitude results in a change of series of social-financial character, such as the dense urbanization, the consumers' movement and the criminalization of the medical profession which is reinforced by the involvement of insurance companies. Progress made in healing cancer and therefore a decrease of the fear of diagnosis may be convincing factors of this change of attitude in briefing [28]. Finally, another essential factor seems to be the alteration of the family from the extended traditional type to a more nuclear one.

Conclusions

Oncology boards should be part of the routine function in all hospitals treating cancer patients. Unfortunately the procedure which should be followed to deal with this health problem has some deficiencies.

The Greek Ministry of Health and Social Solidarity (Ministerial decree 141758/12.11.2010) for the structure of the cancer centers dealing with cancer diagnosis and treatment, refers also to submitted proposals with respect to the restructure of oncologic boards [29].

Furthermore, the above amendments make reference to the control / assessment and records keeping in the oncology departments.

In addition, the responsibility of the function the oncology department is given to the Hospital's oncology committee, aiming to provide better services [29].

As far as cancer patients are concerned, the physician is obliged to conform to the patients' rights according to the directive of the European Union, the Hague Declaration and the article 47 of the Greek Law 2071/92 [30].

With the current mentality, hiding the truth from the patient is wrong and unethical. However, in the Greek society this is not the case as it seems not right to adopt foreign practices. On one hand, informing relatives is ambiguous but on the other hand the continuation of this informational policy is wrong.

So the best solution would be the integration of the positive elements of the patient's awareness and the beneficial effects of the involvement of the Greek family upon one of its members. Thus, the best process for an oncological council should be a flow chart with the alternatives of one or more treatment options, whereas the main aspect should be the inclusion of the patient himself in the procedure of treatment decision. In other words the patient should be aware of his treatment effectiveness as well as of its toxic potential, and the oncological board should co-decide with the patient for the treatment options. This is in accordance with the good medical practice [31], aiming also to the patients' consent, which, no doubt, will lead to the reduction of malpractice (Figure 1) [21]. Further research on the impact of patient decision would improve the structure and the functionality of oncologic boards. In the future, the research should focus on the development of certain guidelines for the integration of expert's opinion and patient's decision.

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LETTERS TO THE EDITOR

Triple negative endometrial cancer may be more sensitive to platinum based chemotherapy

Dear Editor,

Endometrial cancer is the most common gynecologic cancer in the developed world. In 2011, the mortality rate was 1.7-2.4 per 100,00 women. In the United States, as with other developed countries, 46,470 new cases and 8,120 deaths were due to this disease in 2011 [1,2]. Endometrial cancer is divided into type I and II subtypes. Type I is associated with a hyperestrogenic state and usually occurs in obese women, tend to be well differentiated and is identified in early stages. Type II, which is not associated with hyperestrogenism, is usually seen in thin women and is diagnosed in advanced stages. Most endometrial cancers are low-grade, early-stage and carry an excellent prognosis. On the other hand, the 5-year survival of advanced stages (stage 3 and 4) ranges between 23 and 67%.

Breast cancer is also one of the most frequent malignancies in women. The lifetime risk for breast cancer in the United States is usually about 1 in 8 (12%) of women by the age of 95, with 1 in 35 (3%) chance of dying from breast cancer [3]. Breast cancer can be divided in subgroups based on immunohistochemical staining. The group that lacks estrogen receptor (ER) and progesterone receptor (PR) expression and shows absence of HER2 protein overexpression is known as the triple negative phenotype (TNP). TNP breast cancers are more aggressive, have a high proliferation rate, high nuclear grade, frequent p53 overexpression, are more likely to show distant metastasis, and have poorer outcomes, including shorter disease-free and overall survival [4]. TNP breast cancer (TNBC) cells exhibit an abundance of DNA aberrations, suggesting that their DNA repair mechanisms are defective. Consequently, these tumors are theorized of having an increased sensitivity to agents that cause interstrand DNA breaks (e.g., platinum agents). As such, the sensitivity of TNP breast cancers to platinum-based chemotherapy has been the focus of several recent clinical trials in the neoadjuvant/adjuvant and advanced disease settings. A study conducted by Sirohi et al. has retrospectively evaluated the efficacy of platinum-based drugs in 143 metastatic breast cancer patients. Among these, 93 (63.7%) were TNP. The objective response rate was 33.3% in the TNBC group vs. 22% in the non-TNBC (p=0.1) although no difference in OS, PFS and response duration was observed [5]. To summarize, as platinum-based treatments are effective in TNBC, we expect them to be also effective in TNP endometrial cancer. Larger studies conducted in such TNP populations to search effectiveness of platinum-based chemotherapy are needed.

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High dose chemotherapy with autologous stem cell transplantation for patients with germ-cell cancer

Dear Editor,

Germ cell tumors (GCTs) practically represent the only kind of solid tumors that are curable by chemotherapy even when metastatic. This is largely due to their chemosensitivity. Although most of these tumors are cured with the first – or - second-line chemotherapy, patients who experience more than two relapses, or are refractory to all therapy lines, usually die from this disease. The bad prognosis of these patients had urged researchers to search for other treatment options, and having in mind the chemosensitivity of GCTs, a logical step was to increase the doses of cytotoxic drugs and try to overcome the resistance with high-dose therapy [1]. In a retrospective study published in 2008 Einhorn et al. stressed that high-dose protocols for metastatic GCTs can cure a certain number of patients even after multiple relapses [2]. After the publication of this study, our Institute also introduced this procedure using a modified TAXIF protocol of the Tenon hospital, Paris [3,4]. The final confirmation of the activity of high-dose chemotherapy was the last year's retrospective study by Lorch et al. [5] where in 1984 patients they proved that in relapsed GCTs high-dose therapy, followed by autologous hematopoietic stem cell transplantation leads to longer survival when compared to conventional chemotherapy.

During 2008-2010 we performed 11 transplantations in 8 heavily pretreated patients who were previously administered a median of 4 (range 3-4) chemotherapy lines. We used a modified TAXIF protocol, which includes mobilization of stem cells by administering the submyeloablative protocol paclitaxel 250 mg/m^2 and epirubicin 100 mg/m^2 with G-CSF 10 mcg/kg. After mobilization, a large-volume apheresis was performed until the harvested number of cells was enough for two transplantations. The high-dose protocol was the combination of carboplatin AUC 4 daily for 5 days plus etoposide 300mg/m^2/day, days 1-5. The median number of the administered stem cells per transplantation was 3.6x109 (range 1.9-4.5) CD34+ cells per kg of body weight. The median time for neutrophils engraftment was 10 days, and for thrombocytes 13 days. There were no therapy-related deaths. The most frequent grade 3 / 4 toxicities were febrile neutropenia (100% of patients), thrombocytopenia (100%), colitis / diarrhea (63%), nausea (54%) and oral mucositis (45%). One patient developed veno-occlusive liver disease, while 2 patients developed grade 4 infections (facial phlegmon and one septic shock). Overall clinical benefit rate was 62.5% (37.5% PR, 25% SD). No complete remissions were seen. Median survival was 11 months (range 4-20). High-dose chemotherapy with stem cell transplantation represents an option for heavily pretreated patients with GCTs and is feasible at our Institute, which may be one of the reference centers for this kind of treatment in the Balkans. The treatment results in this group of patients is poor, so earlier intensification is mandatory.

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Colon involvement in a chronic lymphocytic leukemia patient

Dear Editor,

Chronic lymphocytic leukemia (CLL) is the most frequently observed type of leukemia in patients older than 50 years. The prognosis of this disease is much better when compared to other leukemia types [1]. Although CLL primarily involves the bone marrow, extramedullary tissues may also be affected. In CLL patients, gastrointestinal involvement is usually seen in Richter syndrome, which is the disease transformation into large B cell lymphoma [2]. The prognosis worsens in such cases.

A 61-year-old woman presented to our outpatient department with stomach ache in the midline. Physical examination revealed no lymphadenopathy or hepatosplenomegaly. Lab tests revealed white blood cell count 25890 mm^3, lymphocyte count 18290 mm^3, hemoglobin level 14.2 g/dl, platelet count 208000 mm^3, lactate dehydrogenase level 454 IU/dl, while peripheral blood smear demonstrated 72% mature lymphocytes with occasional basket cells. Bone marrow aspiration and biopsy were performed and were consistent with CLL (60% B lymphocytes, CD 20 (+), CD 79 (+), CD5 (+)). A flow cytometry performed showed CD5 90% CD23 80%, indicating that the sample comprised of leukemic cells. Abdominal CT scan revealed thickening of the wall of the transverse colon, after which a colonoscopy was performed. In colonoscopy, the transverse colon mucosa was, in general, minimally edematous, granular and in the rectum there were numerous apparent Peyer plaques. Biopsies were obtained from the rectum and transverse colon which were consistent with chronic lymphocytic colitis. Microscopically, dense mucosal and submucosal lymphocytic infiltrates were detected in the transverse colon, and 4/7 biopsies of the colon, showed predominance of small CD20 positive lymphocytes. The cells stained positively also for CLL-associated antigens CD5, CD23, and CD43, but were negative for mantle cell-associated antigen cyclin D1. The patient was considered stage 0 CLL with colon involvement. Gastrointestinal involvement is not common in CLL. Colon involvement without Richter syndrome has rarely been reported in the literature. Arkila et al. [3] have reported a 69-year-old man with CLL and anemia in whom colonoscopy was macroscopically normal, but the histological specimens revealed lymphocytic leukemia in the ileum and colon. In our patient we also have demonstrated colon involvement without Richter syndrome. CLL may cause upper gastrointestinal haemorrhage by directly infiltrating the gastroesophageal junction or through bleeding from oesophageal varices caused by CLL-associated splenomegaly and portal hypertension. According to one case report [4], protein-losing enteropathy may be found in CLL patients. Reports also mention gastrointestinal CLL manifestations such as infiltration of the intestinal mucosa in the small bowel as well as CLL presenting as colitis. CLL, especially after Richter transformation, can cause signs and symptoms suggestive of chronic inflammatory bowel disease. Other rarely described CLL manifestations include intussusception, even perforation of the colon and can also form a route

for infectious complications. The histopathologic differential diagnosis of common benign lymphatic hyperplasias and various malignant lymphoid disorders of the intestine may be challenging. The diagnostic range for CLL should include CD20+/CD5+ coexpression with CD23+ phenotype, and negative staining pattern for Cyclin D1 to exclude mantle cell lymphoma. Differential diagnosis of indolent CD5 negative B-cell lymphomas include follicular lymphoma, which usually has CD10+ phenotype, whereas mucosa-associated marginal zone lymphoma lacks specific phenotypic markers and its immunophenotypic diagnosis is mainly based on exclusion. Lymphoepithelial lesions and plasmacytic differentiation are suggestive of MALT-lymphoma [5].

In conclusion, also gastrointestinal evaluation should perhaps be part of a complete assessment of the treatment response and remission status in CLL patients in whom the colon was originally involved. In CLL patients with gastrointestinal symptoms, an endoscopic evaluation must be performed, and biopsies must be obtained from suspicious regions. The fact that CLL patients may have gastrointestinal involvement without Richter syndrome must be kept in mind.

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A simple technique for vacuum drainage of the peritoneal cavity for the management of anastomotic leaks in patients with gastrointestinal malignancies

Dear Editor,

In cancer patients, any anastomosis along the gastrointestinal tract carries the risk of an anastomotic leak, the incidence of which can be as high as 20%, depending on several and specific local and systematic factors [1]. Following an anastomotic leak, the content of the gastrointestinal tract accumulated into the peritoneal cavity can lead to generalized peritonitis, intraperitoneal abscess formation or it can be drained through the abdominal wound, predisposing to abdominal wall infection and wound dehiscence. Sometimes gravity is not enough for the drainage of the accumulated content and the application of a negative pressure has been proposed as an effective method for the drainage of anastomotic leaks [2].

Between January 2005 to December 2010, 6 patients who were operated on either electively or as an emergency for gastrointestinal tract malignancies and developed gastrointestinal anastomotic leak, were treated with a simple technique for vacuum drainage of the peritoneal cavity after the diagnosis of gastrointestinal leak. In all cases the edge of either the silicon or the PVC tubes was connected to the vacuum pump system (Basic 30 Aspirator, Medela, Illinois, USA) and -20kPa (-150 mm Hg) negative pressure was applied. The -20kPa vacuum pressure was chosen, since we noticed that greater pressures collapsed the lumen of the silicon tubes. We also noticed that the simple connection of the cannula of an ileostomy

Table 1. Details of the gastrointestinal leaks and the application of the proposed vacuum system

Sex/Age (years)	*Brief clinical history*	*Diagnosis of leak*	*Period of VS application (days)*	*Type of fistula finally formed*	*Healing of the fistula (weeks)*
M/86	Disseminated descending colon cancer. Palliative procedure	Enteric content through the intra-operatively placed drain tube and the surgical incision	5	Entero-cutaneous	8
M/54	Splenic flexure colon cancer. Curative operation	Smelly gas but no faecal content through the drain tube	2	Feacal-cutaneous	2
M/51	Disseminated descending colon cancer. Palliative procedure	Enteric content through the lower third of the surgical incision	6	Entero-cutaneous	14
M/62	Cecal adenocarcinoma. Curative operation	Abdominal CT scan revealed a subhepatic abscess infiltrating the right lateral abdominal wall	3	Entero-cutaneous	8
M/75	Pancreatic head adenocarcinoma. Curative operation	Bile through the upper third of the surgical incision	3	Bilio-cutaneous	4
M/77	Rectosigmoid junction cancer. Curative operation	The three lowermost metallic staples for skin approximation were removed leaving a 3cm cutaneous opening	4	Feacal-cutaneous	4

M: males, VS: vacuum system

bag to the vacuum system was similarly insufficient, since the application of even the minimum vacuum pressure (-9kPa) collapsed the bag. Thus, in cases of enteric content drainage through the surgical incision we preferred the air-tightly secure placement of either PVC (N=2) or soft silicon drain tubes (N=1) via the colostomy bag up to the dermal gap and connection of the drain tubes to the vacuum system. With this technique the inflamed, ischemic or necrotic tissues of the abdominal wound were drained into the bag, while the gastrointestinal tract content was driven away of the wound into the vacuum system collector. The vacuum was applied continuously throughout the day and the gastrointestinal content output was recorded every 24 hours. The vacuum was disconnected when less than 30mL of gastrointestinal tract content drainage was recorded within 24 hours and when obvious improvement of the local signs of inflammation was noticed.

Patient characteristics, details of the gastrointestinal leaks and the application of the proposed vacuum system are shown on Table 1. All fistulae were healed spontaneously within 3-14 weeks (median 6). None of the patients developed generalized peritonitis, abscess formation or would dehiscence. A single fistula was successfully crated in all patients and none of the patients developed adverse events while all abdominal wounds were healed uneventfully.

Vacuum assisted closure (VAC) therapy represents a well-established effective treatment option for the treatment of infected wounds, traumatic open abdominal wounds, wounds with bone exposure, pressure ulcers, diabetic foot ulcers and ulcers arising from venous ectasia in the extremities. The method is contraindicated or should not be applied in unexplored or non-enteric fistulae, in wounds with necrotic tissue, in the treatment of osteomyelitis, over actively bleeding tissues, over wounds

being in contact with exposed blood vessels or organs, in previously irradiated or sutured vessels or organs, or in patients treated with anticoagulants [3]. However, the application of the negative pressure for the management of enterocutaneous fistulae arising within an open abdomen still remains controversial with various reports favoring [4] and other being against its use [5].

In conclusion, the application of low vacuum pressure on the distal end of either the intraoperatively placed silicon drain tubes or the newly placed PVC tubes can desirably lead to an enterocutaneous fistula formation through a single point, disrupting the unfavorable sequences of the leak.

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Frequency of thyroid disease among breast cancer patients: a descriptive study of breast cancer patients

Dear Editor,

Currently, there are numerous studies on the relationship between breast cancer and thyroid disorders. Although the exact mechanism of the relationship remains unclear, many studies have shown that thyroid diseases are common among women with breast cancer [1,2]. Some investigators have suggested increased breast cancer risk in patients treated for thyroid disorders, but others believe that there is no association between thyroid diseases and risk of breast cancer [3].The purpose of this descriptive study was to examine the frequency of thyroid disease among breast cancer patients and to compare patient and tumor characteristics in patients with and without thyroid disease.

We retrospectively analysed the medical records of breast cancer patients diagnosed between 2004 and 2012 in Hacettepe University, Institute of Oncology. We examined the frequency of patients with known thyroid diseases including hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis and multinodular goiter and searched patients with suspected thyroid diseases. We evaluated tumor size, tumor grade, estrogen and progesterone receptor status, HER-2 expression and histology of primary tumors. Pearson's chi-square test was used for statistical analysis. A value of $p<0.05$ was considered statistically significant.

Among 2218 patients with breast cancer, 445 (20.1%) cases with thyroid diseases were found. The majority had multinodular goiter (7.9%, N=177) and diffuse goiter (6.9%, N=153). The incidence of other thyroid disorders are shown in Table 1. There was no statistically significant difference in patient and tumor characteristics between patients with and without thyroid diseases.

The relationship and coincidence of breast cancer

Table 1. Distribution of thyroid diseases and thyroidectomy in breast cancer patients

Thyroid disease	*N*	*%*
Multinodular goiter	177	7.9
Diffuse goiter	153	6.9
Hashimoto's thyroiditis	20	0.9
Thyroid cancer	9	0.4
Toxic goiter	6	0.3
Thyroidectomy	124	5.6

with thyroid disorders is a subject of extensive debate. In a prospective study, prevalence of autoimmune thyroid disorders in Greek breast cancer patients was found to be higher (43.9%) than in patients with benign breast diseases (19%) and healthy controls (18.4%) [4]. Ron et al. reported that there was a significantly elevated risk of thyroid cancer following breast cancer and breast cancer following thyroid cancer [3].The results of our study also support their conclusion. Our study suggests a fairly frequent occurrence of thyroid disease among breast cancer patients. However, we could not find an association between the presence of a thyroid disorder and any tumor characteristic.

Breast cancer may share some similar etiologic features with thyroid disease. For instance, thyroid and breast, both are under the influence of similar hormones. On the other hand, estrogen may influence the development, physiology and pathology of human thyroid gland [5]. We did not check all breast cancer patients for thyroid disease, we evaluate only patients with known thyroid disease and patients with suspected thyroid disease so there might be an information bias in our study. Given the inconclusive evidence in the literature we believe that further analytical studies in larger populations are clearly warranted. Meanwhile, we suggest oncologists to check for thyroid disease in women with breast cancer.

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HISTORY OF ONCOLOGY

The great surgeon Jean-Louis Faure (1863-1944) and his contribution in the treatment of uterine cancer

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Summary

At the beginning of the 20th century, Professor Jean-Louis Faure, one of the leading surgeons of the innovative Parisian Medical School, published an exhaustive work on uterine cancer. He was the first to perform in France the procedure of total abdominal hysterectomy by median section of the uterus contributing to the evolution of cancer surgery.

Key words: Faure, gynecologic oncology, hysterectomy, surgery

The eminent cancer surgeon Jean-Louis Faure.

Introduction

At the beginning of the 19th century the first hysterectomy attempts ended in bloody failures and the practice was abandoned. In about 1875-1880, the German surgeon Kaltembach reattempts abdominal hysterectomy with operative mortality of around 67%. Therefore, surgeons continued to perform vaginal hysterectomy with low operative mortality (5 -10%), but still without chances of recovery.

Thanks to asepsis, we return to abdominal hysterectomy with the Viennese Ernst Wertheim (1864-1920) who proposed in 1900 a radical therapy of uterine cancer. However, between 1896 and 1905, he loses 20 (22%) of his 90 operated patients. Generally, 466 hysterectomies in total were identified in 1907 by Sobre-Casas and performed since 1898 by 27 surgeons, the operative mortality rate being 25.1% (117 deaths) [1].

The surgical technique of hysterectomy was perfected in 1896, thanks to the French surgeons Faure, Terrier, Poirier and Quénu. Actually, the removal of the uterus, called "radical" or "total", with extirpation of neoplastic lesions in the pelvic tissues and partial resection of the vagina increased the survival rates. In 1899, during the 2nd Congress of the International Society of Surgery, some surgeons claimed cure rates about 20 to 40% and absence of recurrence beyond 5 years [2].

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Faure's Life - Studies - Career

Jean-Louis Faure was born on October 27, 1863 in Sainte-Foy-la Grande, a small town near Bergerac in Gironde, France, which was the little homeland of the eminent physicians Jean-Martin Charcot (1825-1893), Paul Reclus (1847-1914) and Samuel Pozzi (1848-1918). He died on October 27, 1944 in Saint Émilion. His maternal uncle Paul Reclus was professor of surgery in Paris. Faure began his studies in the Protestant College of Sainte-Foy and graduated in the Lyceum Louis-le-Grand in Paris. In 1884, he enrolled in the Faculty of Medicine (Photo). In 1886, he becomes extern in the department of Alexis Legroux (1839-1894), professor of pathology in the Laennec Hospital and in 1887-1890 he becomes an intern. On July 5, 1888, Faure married Madeleine Bourgeois. From this marriage four children were born.

In 1889-91, he was appointed assistant in anatomy and later on lecturer. In 1895, he became hospital physician. In 1898, he obtained the title of associate professor of surgery. In 1899-1904, he was appointed lecturer of the surgical clinic at the Hôtel-Dieu hospital. In 1918, he was designated lecturer of clinical gynecology and in 1919 he replaced the late professor Samuel Pozzi in the chair of clinical gynecology at Broca Hospital. In 1934, he became emeritus professor of surgery.

In 1924, Faure received the insignia of Commander of the Legion of Honor and became member of the French Academy of Medicine. One year later he was elected president of the Surgical Society [3].

Faure's scientific work

Jean-Louis Faure was one of the greatest surgeons of his time. Although he was specialized in gynecology, he presented an interesting work on cancer and left his mark in many surgical techniques such as the extirpation of the parotid glands and the drainage of peritonitis [3].

His name is related to: 1) Faure's needle: needle of round point handle, for ligation of the hypogastric artery. 2) Faure's needle with a lever: variety of lateral Reverdin needle with lever. 3) Faure's operation: surgical technique of subtotal abdominal hysterectomy by uterine hemisection. 4) Faure's clamp: long curved hemostatic forceps. 5) Faure's extra-condylar veins [4]. 6) Faure's and Ionesco vestibule (pre-vestibular funnel): inconstant prolongation of the vestibule of the back cavity of the omentum, to the right of the opening into lesser sac of peritoneum [5].

His publications include: his doctoral thesis entitled The suspensory apparatus of the liver (L'appareil suspenseur du foie), Hepatoptosis and hepatopexy (L'hépatoptose et l'hépatopéxie) published in 1892, Surgery of the Uterine adnexa (Chirurgie des annexes de l'utérus) printed in 1902, Clinical lessons and operative techniques (Leçons de clinique et de techniques opératoires), his famous book Hysterectomy (L'hystérectomie) published in 1906 and Treatise on medical and surgical gynecology (Traité de gynécologie médico-chirurgicale) appeared in 1911 [6].

His work on oncology

In 1896, Faure practiced the first successful hysterectomy in a cancer patient. It was the first operation of its kind performed in France.

In his book entitled Chirurgie des annexes de l'utérus, Faure describes the procedure of total abdominal hysterectomy by median section of the uterus. He points that it is an extremely simple procedure without any risk of damaging the ureter. The surgeon can reverse the uterus giving in the bottom of the pelvis space to maneuver and to reach the adnexa below by taking them off upwards, both right and left. According to Faure, this method collects all the facilities and is the ideal of operative simplicity.

Faure actually improved this surgical technique so that in 1920 he achieved long-term survival in 60% of the cases. He also claimed that hysterectomy was the treatment of choice in cancer of the cervix when the uterus was still mobile [7].

In 1932, he stated that he had successfully removed uterine cancer in 86% of the cases. However, these results involved mainly early-stage uterine cancers.

Moreover, to relieve the suffering of his patients professor Faure in 1891 and professor Mathieu Jaboulay in 1901 used to practice section of the spinal nerves, in order to cut off the sources of pain. These caused such physiological alterations though, that they had to abandon this method [8].

Faure was also involved in the 19th century's debat-

ing issue of cancer contagiousness. He and other great oncologists of his time like Roussy and Delbet did not attach the least importance on this belief, rejecting that theory [8].

Conclusion

Professor Faure revolutionized the practice of hysterectomy opening new horizons of research in cancer surgery. In fact, it was not until the aftermath of the Second World War when the modern fight against cancer begins with the discovery of new chemotherapeutic agents.

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